

REMARKS**The Amendments**

The claims are amended as to matters of form and to clarify the “aryl” and “aralkyl” terms. Support for the latter clarifications is found at page 5, first three paragraphs, of the specification.

To the extent that the amendments avoid the prior art or for other reasons related to patentability, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art or otherwise unpatentable to applicants. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Election of Species and New Restriction Requirement

The Office Action of April 15, 2002, indicated the making of an Election of Species requirement. Under the established Markush practice, upon finding of allowability of the elected species over the prior art the search should be extended to further species. An Election of Species requirement is not a Restriction Requirement. The instant application is a US National Phase application through the PCT, the claims have unity of invention and there has been no case made that the claims lack unity of invention. There should, therefore, be no restriction herein and should be no reason for applicants to have to split their application into multiple filings.

Applicants disagree with the apparent allegation in the Office Action that the claims recite an improper Markush grouping, i.e., not common core.

Claim 1 is not an improper Markush group. M.P.E.P. § 2173.05(h) discusses types of improper Markush claims and applicants' claims are not of the type indicated to be improper therein. All compounds encompassed by instant claim 1 have a common structural core of the formula I. This structural core is rather distinctive and the variable groups thereon are specifically defined and further distinctive. The compounds also are disclosed to exhibit a community of properties as discussed, for example, at page 81+ of the disclosure. Thus, claim 1 meets the requirement for a proper Markush claim and should be examined in accordance with proper Markush procedure rather than be restricted.

It is further noted that the instant claims are not overly broad and that a search of the entire claim scope would not be an undue burden. The common structural core of claim 1 is rather specific and significantly distinguishes the invention. The R groups are variables but they are also specifically defined (see changes above to aryl and aralkyl terms) and are not overly broad. It is urged that the entire scope of invention should be examined here.

Accordingly, the restriction requirement should be withdrawn.

Applicants note that the Office Action states no prior art reads on the elected subject matter. Applicants request clarification whether this statement was made applying to the entire scope of the Group I set forth in the Office Action or only the elected specific species.

The Rejection Under 35 U.S.C. § 101

The rejection of claim 22 under 35 U.S.C. § 101 is rendered moot by cancellation of the claim and its replacement with a method claim.

The Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection under 35 U.S.C. § 112, first paragraph, is respectfully traversed.

Initially, it is noted that not all of the R groups include aryl or aralkyl terms in their definition, as alleged in the Office Action. Only the definitions of R⁴ and R⁵ recite such terms. Regardless, these terms are now clarified in the claims. It is believed that such clarification renders the grounds of rejection moot. The claims are not overly broad as each R group is literally defined by a small number of specific groups. In any event, breadth alone is not a sufficient basis for rejection.

Thus the rejection should be withdrawn.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-20 under 35 U.S.C. § 112, second paragraph, is believed to be rendered moot at least in part by the above amendments. The claims are amended in several respects in the manner suggested in the Office Action to better conform to U.S. practice.

As to the stereoisomers term, it is urged that this is not indefinite. Stereoisomers of the compounds are within the structural formula I and the claim just clarifies that they are included. Mixtures of such stereoisomers are also included since they would be represented by only a single structural formula but having two or more stereoisomeric forms. Stereoisomerism is well known in the art and the meaning of the claim would be well understood by one of ordinary skill in the art.


As to the R⁶ and R⁷ together being an oxygen atom recitation, it is submitted that the meaning is clear since the only possible structure from the two of them together being an oxygen atom is an epoxide group. Carbonyl is not possible since the R⁶ and R⁷ originate from different carbon atoms.

For the above reasons, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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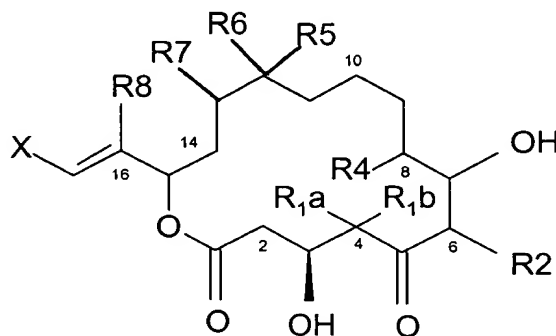
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VERSION WITH MARKINGS TO SHOW CHANGES MADE**IN THE CLAIMS:**

1. (Amended) ~~Epothilone derivatives~~ An epothilone compound of general
formula I,



in which

R^4 means hydrogen, C_1 - C_{10} alkyl, aryl, C_7 - C_{20} aralkyl,

R^5 means hydrogen, C_1 - C_{10} alkyl, aryl, C_7 - C_{20} aralkyl,

wherein, for R^4 and R^5 , aryl is phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl, thiazolyl, which are optionally substituted in one or more places by halogen, OH, O-alkyl, CO_2H , CO_2 -alkyl, $-NH_2$, $-NO_2$, $-N_3$, $-CN$, C_1 - C_{20} alkyl, C_1 - C_{20} acyl and/or C_1 - C_{20} acyloxy groups, and wherein ring heteroatoms can be oxidized, and

wherein, for R^4 and R^5 , aralkyl is benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thienylethyl, or pyridylpropyl, which are optionally substituted in one or more places by halogen, OH, O-alkyl, CO_2H , CO_2 -alkyl, $-NO_2$, $-N_3$, $-CN$, C_1 - C_{20} alkyl, C_1 - C_{20} acyl and/or C_1 - C_{20} acyloxy groups,

R^6 , R^7 each mean a hydrogen atom, together an additional bond or an oxygen atom,

R^8 means a methyl group or hydrogen,

and at the same time, R^{1a} and R^{1b} together stand for a trimethylene group, R^2 stands for a phenyl or benzyl radical, and X stands for a 2-pyridyl, 2-methyl-4-thiazolyl or 2-methyl-4-oxazolyl radical or

at the same time R^{1a} and R^{1b} together stand for a trimethylene group, R^2 stands for a methyl, ethyl or propyl group and X stands for a 2-pyridyl, 2-methyl-4-thiazolyl or 2-methyl-4-oxazolyl radical or

at the same time R^{1a} and R^{1b} in each case stand for a methyl group, R^2 stands for a methyl, ethyl or propyl radical, and X stands for a 2-pyridyl, 2-methyl-4-thiazolyl or 2-methyl-4-oxazolyl radical,

whereby the nitrogen atom and/or the sulfur atom in X can be present in oxidized form, and whereby, if R^2 and R^8 in each case mean a methyl radical, X can be only one 2-pyridyl radical that is optionally oxidized on the nitrogen atom, including all possible stereoisomers as well as their mixtures.

2. (Amended) ~~Compounds~~ A compound according to claim 1, in which R^8 is a hydrogen atom.

3. (Amended) ~~Compounds~~ A compound according to claim 1, in which R^8 is a methyl group.

4. (Amended) ~~Compounds~~ A compound according to claim 1, in which R^2 is an ethyl group.

5. (Amended) ~~Compounds~~ A compound according to claim 1, in which R² is a propyl group.

6. (Amended) ~~Compounds~~ A compound according to claim 2, in which R^{1a} and R^{1b} together mean a trimethylene group.

7. (Amended) ~~Compounds~~ A compound according to claim 3, in which R^{1a} and R^{1b} together mean a trimethylene group.

8. (Amended) ~~Compounds~~ A compound according to claim 6, in which X means a 2-pyridyl radical that is oxidized on the nitrogen atom.

9. (Amended) ~~Compounds~~ A compound according to claim 7, in which X means a 2-pyridyl radical that is oxidized on the nitrogen atom.

10. (Amended) ~~Compounds~~ A compound according to claim 2, in which X means a 2-pyridyl radical that is optionally oxidized on the nitrogen atom.

11. (Amended) ~~Compounds~~ A compound according to claim 4, in which R^{1a} and R^{1b} together mean a trimethylene group.

12. (Amended) ~~Compounds~~ A compound according to claim 5, in which R^{1a} and R^{1b} together mean a trimethylene group.

13. (Amended) ~~Compounds~~ A compound according to claim 11, in which X means a 2-pyridyl radical that is optionally oxidized on the nitrogen atom.

14. (Amended) ~~Compounds~~ A compound according to claim 12, in which X means a 2-pyridyl radical that is optionally oxidized on the nitrogen atom.

15. (Amended) ~~Compounds~~ A compound according to claim 2, in which R² means an ethyl group, R^{1a} and R^{1b} together mean a trimethylene group and X means a 2-pyridyl radical that is optionally oxidized on the nitrogen atom.

16. (Amended) ~~Compounds~~ A compound according to claim 2, in which R² means a propyl group, R^{1a} and R^{1b} together mean a trimethylene group, and X means a 2-pyridyl radical that is optionally oxidized on the nitrogen atom.

17. (Amended) ~~Compounds~~ A compound according to claim 10, in which R² is a propyl group.

18. (Amended) ~~Compounds~~ A compound according to claim 1, in which R⁵ is a methyl group.

19. (Amended) ~~Compounds~~ A compound according to claim 1, in which R^{1a} and R^{1b} in each case stand for a methyl group and R² stands for a methyl or propyl group.

20. (Amended) ~~Compounds~~ A compound of general formula I, of claim 1,
which is: namely

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-9,13-dimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-9,13-dimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-9,13-dimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-10-ethyl-3-(2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-10-ethyl-3-(2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylene)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13Z,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-7-propyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R,3S(E),7S,10R,11S,12S,16S)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R,3S(E),7S,10R,11S,12S,16S)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13E,16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-7-propyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1R,3S(E),7S,10R,11S,12S,16R)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16S)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-N-oxidopyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R,3S(E),7S,10R,11S,12S,16R)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione, or

(1S,3S(E),7S,10R,11S,12S,16S)-10-Propyl-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione.

21. (Amended) ~~Pharmaceutical preparations that contain~~ A pharmaceutical composition comprising at least one compound of ~~general~~ formula I according to claim 1 above as well as a pharmaceutically compatible vehicle.

Claim 22 has been canceled without prejudice or disclaimer.